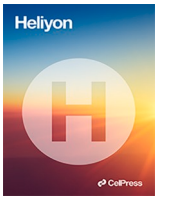
Heliyon 9 (2023) e21902

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



A case report: A new promising treatment for pulmonary sarcomatoid carcinoma - Tislelizumab and Anlotinib combined with local radiotherapy

Ruoxue Cai [a], Ying Liu [a], Huanhuan Sha [b], Jingjing Yu [c], Ying Fang [b,**], Guoren Zhou [a,*], Bo Shen [b]

[a] *Department of Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, 210009 Nanjing, China*
[b] *Department of Oncology, Jiangsu Cancer Hospital, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Institute of Cancer Research, 210009 Nanjing, China*
[c] *Hebei Research Center for Stem Cell Medical Translational Engineering, Hebei Medical University, Hebei Province 050017, China*

ARTICLE INFO

Keywords:
Pulmonary sarcomatoid carcinoma
Immunotherapy
Antiangiogenic therapy
Radiotherapy
Tislelizumab
Anlotinib

ABSTRACT

Background: Pulmonary sarcomatoid carcinoma (PSC) is a rare pathological type of non-small cell lung cancer, only occurs in 0.1%–0.4 % of lung cancer patients. It has a poor prognosis and shows low response to conventional chemotherapy. Target therapy, immunotherapy, and other new approaches are worth exploring in PSC. Recently, patients with MET ex14 skipping mutation can obtain good therapeutic efficacy through target therapy. But there was no definitive treatment for patients without this special mutation.

Case description: Now, we report a female PSC patient without MET ex14 skipping mutation in the cT4N2M1 stage treated with Tislelizumab and Anlotinib obtained remarkable effect for more than 2 years. Significantly, in this case, immunotherapy and antiangiogenic therapy continued to prolong the survival time of more than 10 months for the patient after being treated by local radiotherapy. This is the first case that reported the effectiveness of immunotherapy and anti-angiogenic therapy combined with local radiotherapy in treating PSC and achieved more long-term clinical efficacy than other treatments.

Conclusions: Thus, immunotherapy and antiangiogenic therapy combined with local radiotherapy may bring new hope to advanced PSC patients and is worth conducting further research. It provided an effective reference for the treatment of advanced PSC patients without METex14 skipping mutation. Moreover, this case also demonstrated the synergistic effect of radiotherapy and immunotherapy.

* Corresponding author. Department of Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Baiziting 42, Nanjing, 210009, China.

** Corresponding author. Department of Oncology, Jiangsu Cancer Hospital, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Institute of Cancer Research, Baiziting 42, Nanjing, 210009, China.

E-mail addresses: fangyingnj@163.com (Y. Fang), zhouguoren888@163.com (G. Zhou).

https://doi.org/10.1016/j.heliyon.2023.e21902
Received 10 May 2023; Received in revised form 31 October 2023; Accepted 31 October 2023
Available online 2 November 2023

1. Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare pathological type of non-small cell lung cancer (NSCLC), only occurs in 0.1%–0.4 % of lung cancer patients. It has both epithelial and mesenchymal tumor characteristics, mostly occurs in older men with a history of smoking, and shows a younger trend [1]. Due to its low incidence, poor prognosis, aggressive behavior, and insensitivity to traditional chemotherapy, it is still an intractable clinical problem.

In recent years, with the development of next-generation sequencing (NGS), targeted therapy, and immunotherapy, that still leaves a lot of options for the treatment of PSC. PSC harbors a broad spectrum of mutations, recent studies indicated that inhibition of MET-driven oncogenic pathways had the potential to be a biomarker for PSC-targeted therapy [1,2]. A study suggested that Savolitinib, a highly selective MET inhibitor, achieved relatively good efficacy in patients with METex14 skipping mutation [3]. However, there is currently no established treatment for patients without METex14 skipping mutation.

At present, Li Xu et al. have reported that a PSC patient with high PD-L1 expression (tumor proportion score [TPS]: 60 %, combined positive score [CPS]: 90) was successfully treated with Tislelizumab as monotherapy for more than 8 months of progression-free survival (PFS) [4].

Due to the vascular invasion, the survival time of patients with PSC was reduced. Li et al. reported a PSC patient treated with Apatinib achieved sustained tumor regression [5].

Although PSC shows low response to radiotherapy, the radiotherapy is still essential for PSC local treatment. A case showed that the combination of local radiotherapy and immunotherapy has led to longer outcomes for PSC patients compared with immunotherapy alone [6].

Here, we report a case of advanced PSC patient without METex14 skipping mutation treated with first-line chemotherapy (paclitaxel liposome + cisplatin) and then adjusted to Tislelizumab and Anlotinib combined with local radiotherapy, which is the first case reporting the effectiveness of immunotherapy and angiogenesis inhibitors combined with radiotherapy in the treatment of PSC.

2. Case report

A 57 years old woman with no smoking history coughed accompanied by chest tightness for a month. A physical examination revealed the following: ECOG 1 score, height 155 cm, weight 65 kg, body surface area 1.68m^2.

Chest CT showed that A lesion was seen next to the right lower hilar, with a size of about (3.79 × 5.82cm), considered a malignant lesion. Large lymph nodes are in the mediastinum and right hilus, and the right pleura has thickened locally, which all tended to be a metastasis. In addition, multiple nodules are in the lower lobe of the right lung and the upper lobe of the left lung.

Under CT guidance, a needle biopsy was performed. The biopsy pathology of the right lung showed poorly differentiated carcinoma. Immunohistochemistry showed tumor cells CK7 (+++), CK5/6 (part of+), TTF1 (−), NapsinA (−), P63 (−), P40 (−), Ki67 (about 20 %+), Vim (+), CR (±), D2-40 (+), M.C (part of+), WT1 (part of+) and more like differentiated from epithelial tissue, inclined to poorly differentiated carcinoma. Therefore, the patient was first diagnosed with poorly differentiated carcinoma at stage IVA (cT4N2M1a).

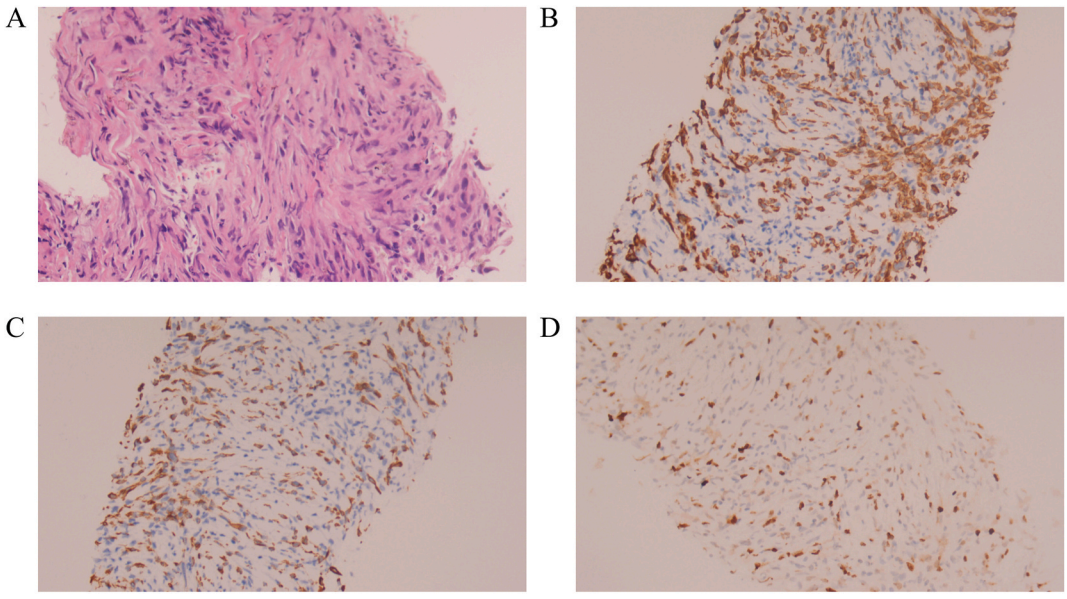


Fig. 1. Hematoxylin-eosin staining and Immunohistochemistry (A–D). (A) Hematoxylin and eosin, (B) AE1/AE3 (+++), (C) CK7 (+++), (D) Ki67 (about 30 %+).

Considering that the patient's disease is in an advanced stage and there was discomfort when eating, she was treated with 6 MVX radiotherapy for subcarinal focus on March 26, 2019 (Dt: 60.75GY/27F). At the same time, she was also treated with paclitaxel liposomes (240mg d1) combined with cisplatin (120mg d1) for two cycles. CT reevaluation showed partial remission (PR), she completed the subsequent 4 cycles of chemotherapy.

Less than one year later, the CT evaluation showed more multiple metastases on the right lung pleura. Under CT guidance, the biopsy of the right pleural nodes showed the presence of dysmorphic cells, and immunohistochemistry showed: spindle cell malignancy, tumor cells S-100 (+), Ki67 (about 30 %+), TTF-1 (−), Desmin (−), AE1/AE3 (+++), CK8 (+), EMA (−), CK7 (+++), CD34 (+), CK5/6 (++), SMA (−), ALK(V) (−) and tended to sarcomatoid carcinoma. Combined with the immunohistochemical result, she was diagnosed with poorly differentiated carcinoma, which was more inclined to be pulmonary sarcomatoid carcinoma finally (Fig. 1).

Then, we also performed genetic testing on the patient's puncture tissue and peripheral blood on May 27, 2020. The results of puncture tissue and peripheral blood NGS (including 674 tumor-related genes) showed a mutation in exon 2 of KEAP1 (KEAP1 c.556G > A p.G186S mutation); TMB was 1.24 mutations/Mb, low TMB; MSS was stable; and MMR gene had no mutation. Because of the patient's will, we did not accomplish the PD-L1 test.

On May 29, 2020, she began treatment with Tislelizumab (200mg, D1) in combination with Anlotinib (12 mg qd, po, D1-D14, q3w).

After two cycles of treatment of Tislelizumab combined with Anlotinib, the patient experienced generalized joint pain, which was assessed as a Grade 2 adverse reaction. This is thought to be an adverse reaction caused by immunotherapy. So, Tislelizumab had to be suspended but the patient continued receiving Anlotinib (12 mg qd, po, D1-D14, q3w). Then after symptomatic treatment, she continued to be treated with Tislelizumab combined with Anlotinib at the original dose in the fourth cycle of treatment. There were no serious adverse reactions occurred again during the subsequent 25 treatments. And the periodic follow-up CT during treatment suggested a partial remission (PR) for efficacy.

Until June 29, 2022, her CT re-examination showed the primary lesion (from 2.78 × 1.50cm to 2.8 × 1.7cm) and pleural lesion (from 1.04 × 0.88cm to 2.5 × 2.0cm) are larger than before. On July 11, 2022, she was treated with 6 MVX radiotherapy for right pleural metastases (IGRT, Dt: 60GY/10F). Meantime, she continued to receive Tislelizumab and Anlotinib treatment for one cycle. On August 31, 2022, the chest CT showed lesions have shrunk again. The efficacy was assessed as PR. After this local radiotherapy, the treatment of Tislelizumab and Anlotinib was continued regularly (Fig. 2) (Fig. 3) (Fig. 4)

Her last re-examination was on March 1, 2023, showed the primary lesion (3.39 × 2.54cm) and the right hilar lymph node lesion (1.24 × 0.93cm) were all progressing. Based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), the lesion was evaluated as a progressive disease (PD). The final PFS for this patient treated with Tislelizumab in combination with Anlotinib was about 33 months.

3. Discussion

At present, with the exploration of immunotherapy, PD-1/PD-L1 and CTLA-4 inhibitors have become promising new options for NSCLC regimens. Researches have indicated that the PD-L1, tumor mutation burden (TMB), and tumor-infiltrating lymphocytes (TILs) have become biomarkers for predicting the positive efficacy of immunotherapy and Yang et al. has found PD-L1(54/148) is highly expressed in PSC [7]. Besides, a retrospective study has manifested that immune checkpoint inhibitors (ICIs) showed high antitumor effects in PSC patients (with the overall response rate of 40.5 %, the disease control rate was 64.8 %, and the median overall survival was 12.7 months (15/37)) [8]. All these offers hope for immunotherapy in PSC.

The vascular invasion is one reason for the poor prognosis associated with PSC. Although the mechanism of angiogenesis is poorly explored for PSC, several studies have reported that PSC patients treated with Apatinib or Anlotinib achieved inhibition of tumor progression [9,10].

Moreover, Elizabeth Allen et al. has shown that the combination of antiangiogenic therapy and immunotherapy can increase the expression of PD-L1, cytotoxic T cell (CTL) infiltration, and resist tumor angiogenesis [11].

Besides, different doses of radiotherapy can intervene with immunotherapy. A study has reported that low-dose radiotherapy changes the tumor microenvironment (TME). It triggers DNA damage and IFN response. Low-dose radiotherapy also upregulates cytokines, inflammatory chemokines, immune checkpoints and CD40. Moreover, it has been demonstrated that radiotherapy

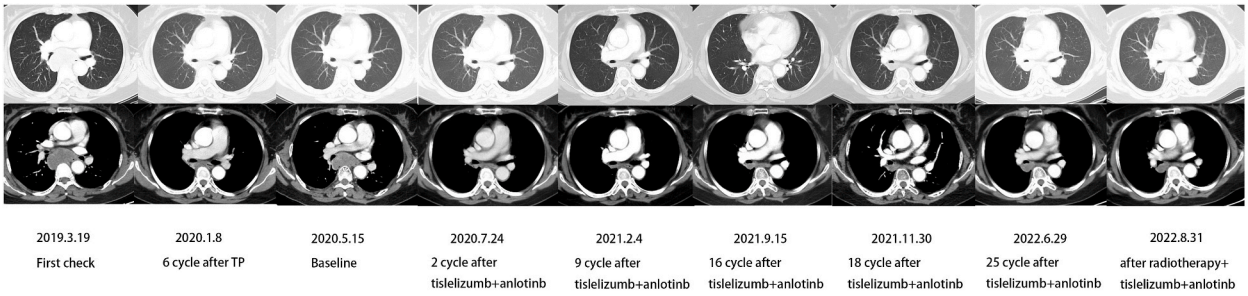


Fig. 2. The sequence of primary lesion computed tomography (CT) scan changes across Tislelizumb and Anlotinb.

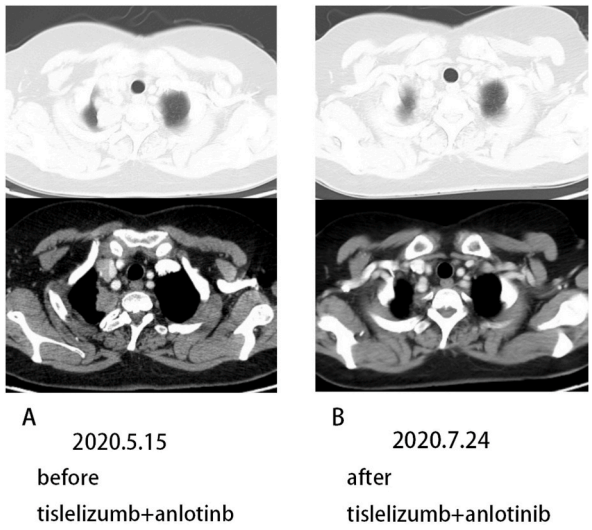


Fig. 3. Comparison of the size of pleural metastases before and after Tislelizumb and Anlotinb treatment (A–B). (A) before Tislelizumb and Anlotinb treatment, (B) after Tislelizumb and Anlotinb treatment.

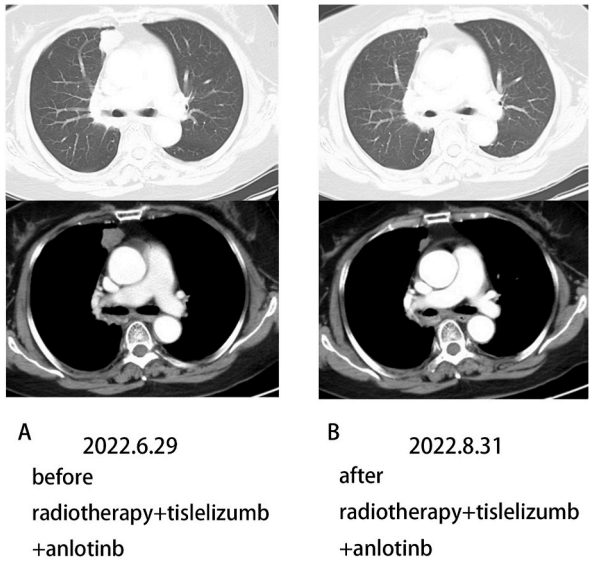


Fig. 4. Comparison of the size of another pleural metastasis before and after Tislelizumb and Anlotinb combined with radiotherapy treatment (A–B). (A) before Tislelizumb and Anlotinb combined with radiotherapy treatment, (B) after Tislelizumb and Anlotinb combined with radiotherapy treatment.

combined with immunotherapy led to the powerful mobilization of antitumor immunity through both effector $CD4^+$ and $CD8^+$ T cells [12]. Significantly, the other study found that high-dose per fraction radiotherapy also induced a rapid increase of tumor-infiltrating myeloid-derived suppressive cells (MDSC) and a subsequent rise of CD8 TILs and circulating CD8 T effector memory cells [13]. Jiao et al. reported a PSC patient with PD-L1 overexpression treated with Toripalimab and local radiotherapy still obtained clinical benefits after getting progression for Toripalimab [6].

In case reports to date, the longest PFS available to patients receiving immunotherapy in combination with antiangiogenic therapy did not exceed 20 months [10,14]. This case report is the first report indicating Tislelizumab combined with Anlotinib obtained about 2 years of PFS in the treatment of PSC. And it is also the first case report to show immunotherapy and antiangiogenic therapy combined with local radiotherapy can get more successful therapeutic effects, and radiotherapy can prolong the effective time of immunotherapy and antiangiogenic therapy. In this case, the patient was treated with Tislelizumab and Anlotinib for 23 months. Then, its primary lesion and right pleural lesion slowly progressed. After receiving localized radiotherapy, she still got more than 10 months of PFS through immunotherapy and antiangiogenic therapy.

Large cohort studies are needed to further study this treatment. In this case, the PD-L1 expression is unknown, so the relationship between the therapeutic effect of Tislelizumab and PD-L1 expression is still unclear. In addition, radiotherapy may promote immunotherapy, but the mechanism of interaction between radiotherapy and antiangiogenic therapy is worth further discussion.

In conclusion, immunotherapy combined with antiangiogenic therapy may be a promising strategy for advanced PSC patients without METex14 skipping mutation. The therapeutic efficacy of this treatment can be augmented by combining modality treatment with local radiotherapy despite local lesion progression. It may bring new hope to advanced PSC patients.

4. Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Data availability statement

Data will be made available on request. The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Funding

This study was funded by the National Natural Science Foundation of China (grant no. 82273162), the National Natural Science Foundation of China (grant no. 82203272), and the National Natural Science Foundation of China (grant no. 82272863).

CRediT authorship contribution statement

Ruoxue Cai: Writing – review & editing, Writing – original draft. **Ying Liu:** Investigation. **Huanhuan Sha:** Supervision, Methodology, Investigation. **Jingjing Yu:** Investigation. **Ying Fang:** Resources, Methodology, Data curation. **Guoren Zhou:** Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation. **Bo Shen:** Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Weissferdt, Pulmonary sarcomatoid carcinomas: a review, Adv. Anat. Pathol. 25 (5) (2018) 304–313.
[2] C. Gong, et al., MET alterations in advanced pulmonary sarcomatoid carcinoma, Front. Oncol. 12 (2022), 1017026.
[3] S. Lu, et al., Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study, Lancet Respir. Med. 9 (10) (2021) 1154–1164.
[4] L. Xu, et al., Use of PD-1 inhibitor tislelizumab in the treatment of advanced pulmonary sarcomatoid carcinoma: a case report, Thorac. Cancer 13 (3) (2022) 502–505.
[5] X. Li, et al., Apatinib-based targeted therapy against pulmonary sarcomatoid carcinoma: a case report and literature review, Oncotarget 9 (72) (2018) 33734–33738.
[6] Y. Jiao, et al., Successful treatment of advanced pulmonary sarcomatoid carcinoma with the PD-1 inhibitor toripalimab: a case report, Oral Oncol. 112 (2021), 104992.
[7] Z. Yang, et al., PD-L1 and CD47 co-expression in pulmonary sarcomatoid carcinoma: a predictor of poor prognosis and potential targets of future combined immunotherapy, J. Cancer Res. Clin. Oncol. 145 (12) (2019) 3055–3065.
[8] C. Domblides, et al., Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma, J. Thorac. Oncol. 15 (5) (2020) 860–866.
[9] F.W. Kong, et al., First-line albumin-bound paclitaxel/carboplatin plus apatinib in advanced pulmonary sarcomatoid carcinoma: a case series and review of the literature, Medicine (Baltim.) 99 (23) (2020), e20667.
[10] Y.F. Li, et al., Case Report: pulmonary sarcomatoid carcinoma complicating TP53 mutation treated successfully with Tislelizumab combined with Anlotinib-a case report, Front. Genet. 13 (2022), 949989.
[11] E. Allen, et al., Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation, Sci. Transl. Med. 9 (385) (2017).
[12] F.G. Herrera, et al., Low-dose radiotherapy reverses tumor immune desertification and resistance to immunotherapy, Cancer Discov. 12 (1) (2022) 108–133.
[13] L. Lin, et al., High-dose per fraction radiotherapy induces both antitumor immunity and immunosuppressive responses in prostate tumors, Clin. Cancer Res. 27 (5) (2021) 1505–1515.
[14] T. Li, et al., Case Report: PD-L1-negative advanced bladder cancer effectively treated with anlotinib and tislelizumab: a report of two cases, Front. Oncol. 13 (2023), 1164368.